UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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APR 2 1 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Sodium N-methyldithiocarbamate (Metam Sodium): Review of Toxicology Data Submitted by the Registrant.

ToxChem No: 039003
Submission: S427888
MRID No: 421173-02
DP Barcode: D183775

FROM: Timothy F. McMahon, Ph.D., Toxicologist 4/8/93
Review Section I, Toxicology Branch II
Health Effects Division (H7509C)

TO: Tom Myers / PM 52
Special Review and Reregistration Division (H7508W)

THRU: Yiannakis M. Ioannou, Ph.D., Section Head Y M Ioannou 4/12/93
Review Section I, Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia Van Gemert, Ph.D., Branch Chief
Toxicology Branch II
Health Effects Division (H7509C) M Van Gemert 4/19/93

Registrant: Metam Sodium Task Force

Action Requested: Review of a subchronic toxicity study with metam sodium in rats.

1 of 18

Conclusions:

A study entitled, "Metam Sodium: 90-Day Drinking Water Study in Rats," was submitted for review by the Metam Sodium Task Force. This study was conducted at ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, and was completed on 10/26/91.

In this study, Metam sodium was administered to male and female rats in drinking water at nominal dose levels of 0, 0.018, 0.089, and 0.443 mg/ml (1.7, 8.1, and 26.9 mg/kg/day in males; 2.5, 9.3, and 30.6 mg/kg/day in females). At the high dose in both sexes, systemic toxicity in the form of significantly decreased food and water consumption, decreased body weight gain, and histological changes in the nasal cavity olfactory epithelium were observed. At the high dose, renal tubular dilatation and basophilia, along with increases in blood, protein, and red cells in urine was also observed. In high dose males, an increased incidence of plasma cell hyperplasia in cervical lymph nodes was demonstrated as well as a significant decrease in platelet count. A significant decrease in group mean body weight was observed in female rats at the mid dose, and body weight gain was decreased 11% at this dose for the duration of the study. Significant decreases in red cell count and hematocrit were also observed at the mid dose in both male and female rats.

Tentative NOEL = 1.7 mg/kg/day (males); 2.5 mg/kg/day (females)

Tentetive LEL = 8.1 mg/kg/day (males; hematological changes); 9.3 mg/kg/day (females; decreased absolute body weight).

Tentative Maximum Tolerated Dose = 26.9 mg/kg/day (males); 30.6 mg/kg/day (females); decreased absolute body weight, body weight gain; alterations in hematology and clinical chemistry parameters; increased incidence of histopathological abnormalities.

Classification:

supplementary

This study does not satisfy the guideline requirements (§82-1) for a subchronic toxicity study in rats.

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FINAL

DATA EVALUATION REPORT

010100

METAM SODIUM

Study Title:
Metam Sodium: 90-Day Drinking Water Study in Rats

Prepared for:

Office of Pesticide Programs
Health Effects Division
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

March 11, 1993

Principal Reviewer: Patricia A. Bittner — Date 3/11/93
Patricia Bittner, M.S.

Independent Reviewer: William L. McLellan — Date 3/11/93
William McLellan, Ph.D.

QA/QC Manager: Sharon A. Segal — Date 3/11/93
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 2-30
Clement Number: 88
Project Officer. James Scott

B

Subchronic Toxicity Study: Guideline § 82-1

EPA Reviewer: Tim McMahon
Toxicology Branch II,
Health Effects Division

Signature:
Date: 4/12/93

EPA Section Head: Mike Ioannou
Toxicology Branch II,
Health Effects Division

Signature: M. Ioannou
Date: 4/12/93

DATA EVALUATION REPORT

STUDY TYPE: Subchronic study in rats

TEST MATERIAL: Metam sodium

Tox Chem. Number: 780

MRID Number: 421173-02

SYNONYMS: Sodium N-methyldithiocarbamate

STUDY NUMBER: PR0797

REPORT NUMBER: CTL/P/3213

SPONSOR: Metam Sodium Task Force

TESTING FACILITY: ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK

TITLE OF REPORT: Metam Sodium: 90-Day Drinking Water Study in Rats.

AUTHOR: S.L. Allen

STUDY COMPLETION DATE: September 26, 1991

CONCLUSIONS: Metam sodium was added to the drinking water of Alpk:APfSD rats (12 animals/sex/dose) for 90 days at nominal dosage levels of 0, 0.018, 0.089, and 0.443 mg/mL (1.7, 8.1, and 26.9 mg/kg/day in males; 2.5, 9.3, and 30.6 mg/kg/day in females). Evidence of compound-related systemic toxicity was observed with significantly decreased food and water consumption and decreased body weight gain when compared to controls, as well as histological changes in the nasal cavity olfactory epithelium (both sexes, high dose). Kidney demonstrated probable treatment-related effects with an increased incidence of renal tubular dilatation and basophilia (high dose), along with an increase in blood, protein and red blood cells in the urine of treated animals. An increased incidence of plasma cell hyperplasia in cervical lymph nodes was demonstrated in high-dose males; this group also exhibited a significant decrease in platelet count. Tentative NOEL of 1.7 mg/kg/day (males) and 2.5 mg/kg/day (females) and tentative LOEL of 8.1 mg/kg/day (males) and 9.3 mg/kg/day (females) were determined. Tentative MTD was determined to be 26.9 mg/kg/day (males) and 30.6 mg/kg/day (females).

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CORE CLASSIFICATION: Supplementary. This study does not meet the minimum requirements set forth under EPA Guideline Series 82-1 for a subchronic toxicity study in rodents.

A. MATERIALS AND METHODS

1. Test Article Description

Name: Metam sodium

Batch number: BAS 005 00N

Supplier: BASF, Limbugeroff, West Germany

CTL reference numbers: Y06930/007, Y06930/008

Purity: 45.13%

Physical property: Yellow liquid

Stability: Not provided

2. Drinking Water Preparation

Experimental drinking water was prepared daily in 2 liter batches by adding the test material to purified water to achieve the desired concentration. Water used for the solution had been purified using reverse osmosis, and its pH adjusted to 9.0 using sodium hydroxide. The amounts of metam sodium used to prepare 2 liters of experimental drinking water were adjusted for an assumed purity of 45.13% w/w.

Results: Due to analytical problems, quantification of the drinking water was performed ≈1 year after completion of the in-life phase of the study for 3 intervals. Spectrophotometric analysis (Philips PU8800 UV/VIS Spectrophotometer) was performed on selected dose solutions which were found to range from 84.8% to 122.2% of nominal concentrations. Stability determination was outside of acceptable limits, ranging from 29% to 85% of nominal values. Dose solutions corresponding to low- and mid-dose levels were the most unstable, with values <40% of the initial concentration.

3. Animals

Species: Rats

Strain: Alpk:APfSD (Wistar derived) SPF

Age: 6-7 Weeks at study initiation

Weight at initiation of treatment: 148-202 g (males)
131-176 g (females)

Source: Barriered Animal Breeding Unit, ICI Pharmaceuticals, Cheshire, UK

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Group assignment: Animals were acclimated to laboratory conditions for 13-14 days and assigned to the following groups based upon a random card shuffling procedure, without taking into account the initial body weights, such that each litter was represented in every experimental group:

Test Group	Nominal Concentration in Water (mg/mL)	No. of Animals	
		Males	Females
1 Control	0	12	12
2 Low-dose	0.018	12	12
3 Mid-dose	0.089	12	12
4 High-dose	0.443	12	12

Animals were housed 4/stainless steel cage in an environmentally controlled room, with temperature ranging from 16° to 29°C, relative humidity ranging from 51% to 84%, 15 air changes/hour and 12-hour photo period. Rats were supplied with powdered CT-1 diet (Special Diets Services, Ltd, Stepfield, UK).

Rationale for dose selection:

Not provided

4. Statistics

All analyses were carried out using the GLM procedure in SAS (1985). Least square means were calculated using the LSMEAN option in SAS PROC GLM. Unbiased estimates of differences from control were provided by the difference between each treatment group least square mean and the control group least square mean. A two-sided Student's t-test was used to compare each treatment group least square mean with the control least square mean to determine statistical differences from control. The following statistical tests were used:

--- Initial body weights, weekly water consumption, weekly food consumption, hematology, blood and urine clinical biochemistry, organ weights--analysis of variance.

--- Body weights (other than day 1)--analysis of covariance with initial body weight as covariate; organ weights--analysis of covariance with final body weight as covariate.

5. Quality Assurance

A quality assurance statement was signed and dated September 23, 1991.

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B. METHODS AND RESULTS

1. General Observations

Animals were observed daily for mortality, morbidity and clinical signs of toxicity. A detailed clinical examination was performed daily during the first five weeks of the study, then weekly for the remaining eight weeks.

Results: One high-dose female was euthanized in extremis on day 5. Necropsy revealed cystitis, gramulocytic hyperplasia (sternal marrow), unilateral hydronephrosis, pyelonephrosis, lymphadenitis, gastric hemorrhagic foci, hyperplasia of the ureter, and inverted thymus. Among other animals, there were increased incidences of nasal staining (all dose levels, males; high-dose females), subdued behavior (high-dose males and females), urinary incontinence and thin body (high-dose females) when compared to controls. All other effects did not appear to be treatment related.

2. Body Weights/Food and Water Consumption/Test Material Intake

Body weight data were recorded weekly throughout the study and at study termination. Food and water consumption data were recorded weekly for each cage of rats.

Body weights: Table 1 presents mean body weights at weeks 1, 7, and 14, and mean body weight gains between weeks 1 and 7, 7 and 14, and 1 and 14. Mean body weights were significantly (≈22%) decreased during weeks 1-14 in high-dose males and females, and ≈4% during weeks 5 and 7-14 in mid-dose females, when compared to control values. With regard to body weight gain, low-dose animals were unaffected by the compound when compared to controls; high-dose animals demonstrated dramatic decreases, when compared to control values, of 45 and 63% during weeks 1-7, and 37 and 49% during weeks 1-14 in males and females, respectively.

Food and water consumption: Table 2 presents mean food and water consumption data at selected intervals throughout the study. Significant decreases in mean food consumption (g/animal/day) were noted throughout the study in high-dose males (≈20-36%) and females (≈20-50%), when compared to controls. Significant changes in mean food consumption at other doses were assessed to be incidental. Weekly water consumption values were significantly decreased in mid-dose females ($p \leq 0.05$ or 0.01) and in high-dose males and females ($p \leq 0.01$) throughout the study when compared to controls.

Test article intake: Test article intake cannot be accurately determined due to the instability of the test material, and the lack of characterization during the in-life phase of the study. Target intake levels based on weekly mean water consumption and the nominal levels of metam sodium in drinking water over the entire study period were stated by the registrant as 1.7, 8.1, and 26.9 mg/kg/day in males, and 2.5, 9.3, and 30.6 mg/kg/day in females, for the low-, mid-, and high-dose groups, respectively.

3. Ophthalmoscopic Examination

Ophthalmologic examinations were conducted prior to study initiation and during study week 13, using an indirect ophthalmoscope after topical administration of a mydriatic agent.

Results: One high-dose male exhibited vitreal hemorrhage during week 13, but this finding appears to be incidental as it was also seen in one female pre-experimentally.

4. Clinical Pathology

Blood was collected at termination by cardiac puncture. Urine was collected over an ≈18-hour period from animals during the week prior to termination. During the urinary collection period, animals were housed in individual metabolism cages and denied access to food and water. The checked (X) parameters were examined.

(a) Hematology

X Hematocrit*	X Leukocyte differential count*
X Hemoglobin (HGB)*	X Mean corpuscular HGB (MCH)
X Leukocyte count (WBC)*	X Mean corpuscular HGB concentration (MCHC)
X Erythrocyte count (RBC)*	X Mean corpuscular volume (MCV)
X Platelet count*	X Prothrombin time*
Reticulocyte count (RETIC)	X Kaolin-cephalin time
X Red cell morphology	

*Recommended by Subdivision F (November 1984) Guidelines

Results: Selected data for hematology parameters are presented in Table 3. A slight but significant ($p \leq 0.05$; 9%) decrease in the platelet counts of high-dose males compared to controls were noted, but none were found in females. For other hematology parameters (hemoglobin, hematocrit, red cell volume, red blood cell count, mean cell volume, mean cell hemoglobin, eosinophil count), some deviations from control values reached a level of significance. However, these changes were not considered to be of toxicological importance since they were either within normal ranges or sporadic.

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(b) Blood (Clinical) Chemistry

Electrolytes

X Calcium*
X Chloride*
Magnesium
X Phosphorus*
X Potassium*
X Sodium*

Enzymes

X Alkaline phosphatase (ALP)
Cholinesterase
X Creatine phosphokinase
Lactic acid dehydrogenase
X Serum alanine aminotransferase (SGPT)*
X Serum aspartate amirotransferase (SGOT)*
X Gamma glutamyltransferase (GGT)

Other

X Albumin*
Albumin/globulin ratio
X Blood creatinine*
X Blood urea nitrogen*
X Cholesterol (total)
Globulins
X Glucose*
X Total bilirubin*
Direct bilirubin
X Total protein*
X Triglycerides

*Recommended by Subdivision F (November 1984) Guidelines

Results:

Selected data for mean clinical chemistry parameters are presented in Table 4. Plasma urea was significantly increased above control values in high-dose females and numerically increased in high-dose males, probably owing to slight dehydration among these animals. Significant alterations from control values were noted in plasma alanine transaminase, aspartate transaminase, and alkaline phosphatase in high-dose males, and plasma phosphorus, sodium, chloride, cholesterol and triglycerides in high-dose females; however, they all appeared to be within normal ranges for these animals. Effects on plasma glucose cannot be evaluated since it does not appear that the animals were fasted prior to blood collection, as per Guidelines.

(c) Urinalysis

X Appearance
X Volume
X Specific gravity
X pH
X Sediment (microscopic)
X Protein
X Glucose
X Ketones
Bilirubin
X Blood
Nitrate
X Urobilinogen

Results: Selected urinalysis parameters are presented in Table 5. Urine volume was significantly decreased in high-dose males (49%) and in mid- and high-dose females (30 and 35%, respectively) compared to control values. Specific gravity was slightly yet significantly increased in high-dose males, and in mid- and high-dose females. Urine pH was significantly (6%) decreased in high-dose males. These changes were probably due to a slight dehydration from decreased water consumption as well as being fasted for ≈18 hours during the period of urine

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collection. Qualitative urinalysis demonstrated an slight increase in the presence of blood in the urine in some males (all doses), however, the magnitude of this change was not the same for all males, and not all males were affected. Increasing the dose of the test article might have resulted in an increase in the severity of response, but not the numbers of rats affected. There were increased numbers of animals (both sexes) exhibiting renal epithelial cells in the urinary sediment at mid- and high-dose, and slightly increased numbers of females (all doses) exhibiting red and white blood cells in urinary sediments. All other changes did not appear to be treatment related.

5. Sacrifice and Pathology

All animals were euthanized at the scheduled time of necropsy, except one female which was euthanized on study day 5. Animals were exsanguinated after being anesthetized with halothane BP vapor, and subjected to a full post-mortem examination. The checked (X) tissues/organs were fixed in 10% neutral buffered formalin saline, with the following exceptions: eye and Harderian gland (Davidson's fixative), and testis, epididymis, skin and mammary gland (Bouin's solution). The double-checked (XX) organs were also weighed (paired organs weighed together) for all animals terminated at scheduled necropsy.

	Digestive System		Cardiovascular/Hematologic		Neurologic
	Tongue	X	Aorta*	XX	Brain* (3 levels)
X	Salivary glands*	X	Heart*	X	Peripheral nerve* (sciatic nerve)
X	Esophagus*	X	Bone marrow*	X	Spinal cord* (three levels)
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	X	Spleen*	X	Eyes* (optic nerve)
X	Jejunum*	X	Thymus*		
X	Ileum*				Glandular
X	Cecum*		Urogenital		
X	Colon*			XX	Adrenals*
X	Rectum*	XX	Kidneys*	X	Lacrimal gland
XX	Liver*	X	Urinary bladder*	X	Mammary gland
	Gallbladder*	XX	Testes*	X	Thyroids*
X	Pancreas*	X	Epididymides	X	Parathyroids*
		X	Prostate*	X	Harderian glands
	Respiratory	X	Seminal vesicle	X	Zymbal's gland
		X	Ovaries*		
X	Trachea*	X	Uterus*		
XX	Lungs*				

Other

X Bone (sternum and femur)*
X Nasal passages
X Skeletal muscle*
X Skin*
X All gross lesions and masses*

*Recommended by Subdivision F (November 1984) Guidelines

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Bone, lacrimal gland, eye, Harderian gland, mammary gland, muscle, right sciatic nerve, skin, spinal cord, and Zymbal's gland were stored. All other tissues checked above were embedded in paraffin wax. Sections of these tissues from control and high-dose animals, as well as nasal passages from low- and mid-dose animals were stained and examined histologically.

(a) Organ weights

Significant decreases in mean absolute organ weight occurred in high-dose animals (both sexes) when compared to controls, for all organs weighed, except kidneys (female) and testes. The decreases in absolute organ weight were primarily due to decreased body weight gain, since the relative organ weight remained stable. Furthermore, with the exception of a slight increase in kidney (high-dose females) and liver weights (mid-dose females), there was no significant difference in organ weight adjusted for body weight for any group.

(b) Macroscopic pathology

No treatment-related findings were noted.

(c) Microscopic pathology

A summary of selected histopathological findings is found in Table 6. Nasal cavity alterations were noted in high dose animals, as increased incidences of vacuolated Bowman's glands/ducts (olfactory epithelium), vacuolated olfactory epithelium, disorganization of nasal epithelium (both sexes), and increased incidence of necrosis of nasal cavity (females). Increased incidences of rhinitis, goblet cell hyperplasia, and ulceration were also seen sporadically, but there was no dose-related response. There was also an increased incidence above controls among high-dose animals of plasma cell (females) hyperplasia in cervical lymph node, renal tubular basophilia (males and females), and renal tubular dilatation with eosinophilic casts (males). All other findings were considered incidental. The high incidence of microtubular microlithiasis in both control (12/12) and high-dose (10/12) females, although not treatment related, may indicate intrinsic renal compromise in these animals. Kidney histopathology for low- and mid-dose animals was not performed as per Guidelines. These examinations may have clarified changes observed in these organs at the high dose.

C. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS

Temperature and humidity of the animal rooms were outside of acceptable limits on several "occasions," however no data were provided about the frequency of these occurrences. Although the effects of these fluctuations may have been minimal, it is possible that they were stressful to the animals and contributed to their dehydrated state as detailed below.

Several of the effects observed in the study may be related to the decreased food and water consumption in the high-dose animals when

compared to controls. Water consumption was probably diminished due to the unpalatability of the test material in the water, but may also be treatment related, as was the food consumption. The primary effects of these changes are observed in decreases in body weight and body weight gain at mid dose (females) and high dose (both sexes) when compared to control values. The decrease in urine volume, increase in specific gravity and plasma urea can also be attributed to the decreased water intake. Significant increases in mean cell volume were surprising, since one would expect that a decrease in water consumption would cause a reduction in cell volume; this disparity is probably due to the derived nature of the mean cell volume. [illegible]ency in the study existed in the collection of food and water consumption data which was not performed for individual animals as per Guidelines.

Slightly significant decreases in platelet counts were observed in high-dose males. Glucose levels cannot be reviewed because the animals were not fasted before termination, however, the significant decrease noted in high-dose males was probably due to decreased food consumption. Significant decreases in mean absolute organ weight occurred in both sexes for all organs from high-dose animals that were weighed (except kidneys (females) and testes), when compared to controls. However, these decreases were primarily due to a decrease in body weight gain, since relative organ weight remains stable.

The nasal cavity olfactory epithelium appeared to be systemically sensitive to the test material. Histopathologic changes were observed only at high dose, and correspond with clinical observations of staining around the nose. In addition, kidney appeared to be a target organ, with findings of renal tubular dilatation and basophilia, increases in blood, protein, red blood cells, and renal epithelial cells in the urine in treated animals. Other increased incidences above control values were noted at high dose as hyperplasia in cervical lymph node cells. Kidney as a target organ was not examined histologically in low- and mid-dose groups as per Guidelines; this examination might have clarified possible treatment-related effects.

Although there appear to be compound-related effects due to the changes noted above, it is not possible for the reviewers to ascribe dose levels to them. Analyses of the drinking water were not performed during the conduct of the study due to "analytical problems." Analyses were performed ≈6-12 months after completion of the study. Stability of the test material in the water samples was outside of acceptable limits, for all levels tested, with low- and mid-dose values <40% of nominal concentrations.

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Table 1. Mean Body Weights and Weight Gains (g ± SD) in Rats Fed Metam Sodium for 90 Days in Drinking Water.[a]

Drinking water level (mg/ml)	Mean Body Weight (g) at Week 1	7	14	Mean Body Weight Gain[b] (g) Between Weeks 1-7	7-14	1-14
			Males			
0.000	179.2±12.7	383.0±30.0	464.1±43.7	203.8±24.7	81.1±21.3	284.9±37.2
0.018	183.3±14.2	389.9±22.7	471.9±32.3	206.7±18.6	82.0±17.7	288.7±31.8
0.089	176.6±14.2	370.3±26.1	445.3±38.8	193.7±19.1	75.0±16.5	268.7±32.8
0.443	182.8±13.3	295.5±20.8**	361.5±29.1**	112.7±21.3	66.0±12.7	178.7±28.1
			Females			
0.000	146.0±8.8	239.0±15.9	266.0±17.9	93.0±10.7	27.0±7.6	120.0±13.7
0.018	148.2±7.4	241.3±12.8	268.3±15.7	93.2±9.6	26.9±9.0	120.1±11.0
0.089	150.7±10.9	230.1±20.1**	257.7±19.6*	79.4±15.8	27.6±10.5	107.0±16.1
0.443[c]	147.6±9.6	182.3±16.6**	209.5±17.7**	34.4±12.7	27.3±7.5	61.6±14.3

[a] Based on 12 animals/sex/dose unless otherwise indicated
[b] Calculated by our reviewers, levels of significance not calculated.
[c] Based on 11 animals; one female was euthanized on study day 5.

** Statistically different from control at 1% level; Student's t-test, two sided.
* Statistically different from control at 5% level; Student's t-test, two sided.

Data extracted from CBI report, pp. 41-42, pp. 127-134.

Table 2. Mean Food and Water Consumption for Selected Intervals in Rats Fed Metam Sodium in Drinking Water for 90 Days[a].

Weeks	Water Concentration of Metam Sodium (mg/L)							
	0.000	0.018	0.089	0.443	0.000	0.018	0.089	0.443[b]
	Food Consumption (g/rat/day)							
	Males				Females			
1	25.3	25.7	24.5	16.1**	19.7	20.1	18.7	10.6**
7	26.5	27.6	26.4	21.0**	19.3	19.6	18.5	15.0**
13	23.4	24.3	23.1	19.6**	16.5	17.5*	16.7	13.2**
1-13[c]	26.6	27.2	26.1	20.3	18.9	19.5	18.4	13.9
	Water Consumption (mL/rat/day)							
	Males				Females			
1	27.5	29.7	26.0	12.5**	30.2	26.3	20.7**	8.6**
7	32.8	35.6	33.2	17.8**	35.2	34.8	24.3	12.8**
13	30.2	30.9	29.1	16.2**	29.9	29.8	22.2*	11.6**
1-13[c]	31.9	33.6	31.4	17.1	33.1	31.4	23.1	12.3

[a] Based on 12 animals/sex/dose unless otherwise specified
[b] Based on 11 animals after study week 1, due to euthanization of one female on study day 5
[c] Calculated, but not statistically analyzed, by reviewers
*Statistically significant difference at the 5% level
**Statistically significant difference at the 1% level
Data extracted from CBI report, pp. 43-46.

Table 3. Selected Hematology Results in Rats Given Metam Sodium in Drinking Water for 90 Days.[a]

Parameter	Water Concentration of Metam Sodium (mg/ml) 0.000	0.018	0.089	0.443[b]
		Males		
Hematocrit	0.519±0.015	0.507*±0.021	0.499**±0.017	0.503**±0.021
Platelet count ($x10^9$/L)	539±77	574±63	530±83	489*±50
Red blood cell count ($X10^{12}$/L)	8.74±0.23	8.55±0.33	8.33**±0.31	8.22**±0.33
Mean cell volume (fl)	59.3±1.2	59.3±1.7	59.9±2.0	61.1**±1.8
Mean cell hemoglobin (pg)	18.8±0.5	19.0±0.7	18.8±0.6	19.4*±0.8
		Females		
Hematocrit	0.522±0.020	0.506*±0.022	0.505**±0.021	0.505**±0.009
Platelet count ($x10^9$/1)	568±65	565±72	582±69	561±87
Red blood cell count ($X10^{12}$/L)	8.21±0.30	7.89*±0.33	7.85**±0.32	7.82**±0.28
Mean cell volume (fl)	63.7±1.7	64.2±3.0	64.5±1.8	64.7±2.1
Mean cell hemoglobin (pg)	19.7±0.8	20.2±1.1	20.0±0.7	20.2±1.2

[a] Based on 12 animals/sex/dose unless otherwise indicated

[b] Based on 11 animals; one female was euthanized on study day 5

*Statistically significant difference at the 5% level

**Statistically significant difference at the 1% level

Data extracted from CBI report, pp.51-54.

Table 4. Selected Clinical Chemistry Results in Rats Given Metam Sodium in Drinking Water for 90 Days.[a]

Parameter	Water Concentration of Metam Sodium (mg/ml) 0.000	0.018	0.089	0.443[b]
			Males	
Plasma alanine transaminase (IU/L)	56.1±8.3	52.6±5.3	53.0±9.8	49.1*±7.3
Plasma aspartate transaminase (IU/L)	55.6±6.7	54.3±8.2	56.2±4.4	47.5*±6.6
Plasma alkaline phosphatase (IU/L)	184±23	165±23	183±34	155**±42
Plasma urea (mg/100 mL)	46.1±4.3	45.4±3.8	45.8±3.7	49.3±3.6
			Females	
Plasma alanine transaminase (IU/L)	39.9±12.5	43.0±9.0	39.8±9.3	36.8±7.3
Plasma aspartate transaminase (IU/L)	55.5±9.9	54.4±7.5	59.5±23.0	50.0±6.0
Plasma alkaline phosphatase (IU/L)	94±25	91±29	82±21	109±34
Plasma urea (mg/100 mL)	37.5±8.8	40.6±5.6	40.9±3.9	58.0**±12.8

[a] Based on 12 animals/sex/dose unless otherwise indicated

[b] Based on 11 animals; one female was euthanized on study day 5

*Statistically significant difference at the 5% level

**Statistically significant difference at the 1% level

Data extracted from CBI report, pp.55-58.

Table 5. Selected Urinalysis Results in Rats Given Metam Sodium in Drinking Water for 90 Days.[a]

Parameter	Water Concentration of Metam Sodium (mg/ml) 0.000	0.018	0.089	0.443[b]
		Males		
Urine volume (mL)	7.80±2.55	7.58±1.58	7.52±1.85	3.95±0.49**
Urine specific gravity	1.040±0.004	1.041±0.005	1.041±0.008	1.053±0.005**
Urine pH	6.47±0.19	6.30±0.24	6.27±0.25	6.06±0.09**
Blood[cd]	1(++)	1(+++)	2(+,++)	2(++,+++)
Urinary sediments[c]				
White blood cells	0	2	2	0
Red blood cells	0	1	1	0
Renal epithelial cells	1	0	2	10
		Females		
Urine volume (mL)	4.94±2.07	4.36±1.54	3.46±2.57*	3.19±0.72*
Urine specific gravity	1.041±0.006	1.044±0.006	1.049±0.011**	1.053±0.005**
Urine pH	6.02±0.15	5.94±0.14	6.17±0.57	5.98±0.05
Blood[cd]	0	0	1(+)	0
Urinary sediments[c]				
White blood cells	0	1	1	3
Red blood cells	0	1	1	3
Renal epithelial cells	0	0	2	8

[a] Based on 12 animals/sex/dose unless otherwise indicated
[b] Based on 11 animals; one female was eutnanized on study day 5
[c] Values represent numbers of animals affected
[d] Represents an arbitrary scale of an increasing presence of blood in urine (+, ++, +++)
*Statistically significant difference at the 5% level
**Statistically significant difference at the 1% level
Data extracted from CBI report, pp.59-64.

Table 6. Selected Histological Findings in Rats Fed Metam Sodium for 90 Days in Drinking Water.[a]

	Dose concentration (mg/ml)							
	0.000	0.018	0.089	0.443	0.000	0.018	0.089	0.443[b]
Organ/Lesion	Males				Females			
Nasal Cavity								
Disorganization olfactory epithelium	0	0	0	2	0	0	0	10
Prominent vacuolated Bowman's glands/ducts/olfactory epithelium	0	0	0	5	0	0	0	11
Vacuolation olfactory epithelium	0	0	0	2	0	0	0	11
Necrosis	0	0	0	0	0	0	0	1
Kidney								
Renal tubular basophilia	1	-[c]	-	2	0	-	-	3
Cervical Lymph Node								
Plasma cell hyperplasia	1	-	-	3	1	-	-	0

[a] Based on histological examination from 12 rats/sex/group, unless otherwise indicated

[b] Based on histological examination from 11 rats; one female was euthanized on study day 5.

[c] Parameter and group for which no animals were examined.

Data extracted from CBI report, pp. 75-81.